WDN/SLR:dm 02/02/05 4239-64458-02 350828

PATENT
Attorney Reference No. 4239-64458-02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Negishi et al.

Application No. 10/505,183

Filed: August 18, 2004

Confirmation No. 2375

For: MUTATED CONSTITUTIVELY ACTIVE NUCLEAR ORPHAN RECEPTOR

Examiner: Not yet assigned

Art Unit: 1646

Attorney Reference No. 4239-64458-02

REQUEST FOR CORRECTED OFFICIAL FILING RECEIPT

TO: OFFICE OF INITIAL PATENT EXAMINATION'S
FILING RECEIPT CORRECTIONS
FAX NO.: 703-746-9195
(TOTAL PAGES TRANSMITTED: 10)

Three errors appear in the official Filing Receipt issued for the above-identified patent application, as listed below. Attached is a copy of the official Filing Receipt with the requested corrections handwritten thereon.

1. The number of independent claims should be --2-- instead of "3" as typed on the Filing Receipt. A copy of the claims is attached to show the number of independent claims.

2. Inventor "Masanhiko Negishi" should be --Masahiko Negishi--. A copy of the Declaration of Inventorship signed by Masahiko Negishi is attached to show the correct spelling of his name.

3. In the title of the invention, "Ophan" should be --Orphan--. A copy of the cover page of the published international application is attached to show the correct title of the invention.

Please correct the identified errors and issue a corrected official Filing Receipt.

I hereby certify that this paper and the documents referred to as being attached or enclosed herewith are being facsimile transmitted to fax number 703-746-9195 on the date shown below.

Sheree Lynn Rybak, Ph.D.
Registration No. 47,913

February 2, 2005
Date

cc: Docketing

NIH / SLK / MMS

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10/505,183	08/18/2004	1646	1040	4239-64458-02	2	35	~~3~~ 2

CONFIRMATION NO. 2375

36218
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121 S.W. SALMON STREET, SUITE #1600
ONE WORLD TRADE CENTER
PORTLAND, OR 97204-2988

FILING RECEIPT

"OC000000014981883"

Date Mailed: 01/25/2005

Receipt is acknowledged of this regular Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Filing Receipt Corrections, facsimile number 703-746-9195. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).**

Applicant(s) Masahiko
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Domestic Priority data as claimed by applicant
This application is a 371 of PCT/US03/05163 02/19/2003
which claims benefit of 60/358,500 02/19/2002

Foreign Applications

Projected Publication Date: 04/28/2005

Non-Publication Request: No

Early Publication Request: No

Title

Mutated constitutively active nuclear ~~ophan~~ orphan receptor

Preliminary Class

530

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Title 35, United States Code, Section 184
Title 37, Code of Federal Regulations, 5.11 & 5.15

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We claim:

Independent → 1. A polypeptide encoding a non-constitutively active nuclear orphan receptor (non-CAR) comprising a mutation in a native CAR sequence, wherein the mutation renders the polypeptide less constitutively active.

2. The polypeptide of claim 1, wherein the mutation corresponds to murine CAR (mCAR) position Thr176, mCAR position Leu352, mCAR position Leu353, human CAR (hCAR) position Leu342, and/or hCAR position Leu343.

3. The polypeptide of claim 1, wherein the mutation corresponds to mCAR position Thr176.

4. The polypeptide of claim 1, wherein the mutation corresponds to mCAR position Thr176 and mCAR position Leu352.

5. The polypeptide of claim 3, wherein the mutation is a Thr176 to Val176 (T176V) mutation or a Thr176 to Leu176 (T176L) mutation.

6. The polypeptide of claim 2, wherein the mutation corresponds to hCAR position Leu342 and hCAR position Leu343.

7. The polypeptide of claim 2, wherein the mutation is a Leu352 to Ala352 (L352A) mutation.

8. The polypeptide of claim 2, wherein the mutation is a Leu342 to Ala342 (L342A) mutation or a Leu343 to Ala343 (L343A) mutation.

9. The polypeptide of claim 1, wherein the polypeptide further comprises one or more conservative amino acid substitutions which do not substantially decrease the non-constitutive activity of the polypeptide.

10. The polypeptide of claim 1, wherein the polypeptide confers xenochemical metabolizing activity to a xenochemical-metabolizing enzyme, and wherein the xenochemical metabolizing activity can be detected *in vitro*.

11. The polypeptide of claim 10, wherein expression of the xenochemical-metabolizing enzyme is regulated by an enhancer element.

12. The polypeptide of claim 10, wherein the xenochemical-metabolizing enzyme metabolizes a xenochemical selected from the group consisting of phenobarbital and 1,4-bis [2-(3,5-dichloropyridyloxy)] benzene (TCPOBOP).

13. The polypeptide of claim 1, wherein the polypeptide confers steroid metabolizing activity to a steroid-metabolizing enzyme, and wherein the steroid metabolizing activity can be detected *in vitro*.

14. The polypeptide of claim 13, wherein the steroid-metabolizing enzyme metabolizes a steroid selected from the group consisting of estrogen and estradiol.

15. The polypeptide of claim 1, wherein the polypeptide is purified.

16. A kit comprising the polypeptide of claim 1 and a steroid and/or a xenochemical.

17. A composition comprising the polypeptide of claim 1.

18. An isolated nucleic acid encoding the polypeptide of claim 1.

19. The isolated nucleic acid of claim 18 operably linked to a promoter.

20. A vector comprising the isolated nucleic acid of claim 18.

21. A recombinant nucleic acid comprising the isolated nucleic acid of claim 18.

22. A cell transformed with the recombinant nucleic acid of claim 21.

23. The cell of claim 22, wherein the cell comprises xenochemical metabolizing activity and/or steroid metabolizing activity.

24. A transgenic mammal comprising the recombinant nucleic acid of claim 21.

25. A specific-binding agent which specifically binds to the polypeptide of claim 1, but does not substantially bind to a nuclear orphan receptor CAR.

26. A composition comprising the isolated nucleic acid of claim 18.

Independent → 27. A method of generating a substantially non-constitutively active CAR, comprising:

introducing one or more mutations into a native CAR sequence, wherein the mutation renders the polypeptide substantially non-constitutively active, and wherein the mutation does not significantly interfere with the ability of the native CAR to be induced by a CAR-responsive xenochemical or a CAR-responsive steroid.

28. The method of claim 27, wherein the mutation corresponds to mCAR position Thr176, mCAR position Leu352, mCAR position Leu353, hCAR position Leu342, and/or hCAR position Leu343.

29. A method of screening a test agent to identify agents which activate a xenochemical and/or steroid metabolizing enzyme, comprising:

contacting a cell with the test agent, wherein the cell comprises the polypeptide of claim 1 and a nucleic acid sequence operably linked to an enhancer element; and

detecting the presence or absence of xenochemical and/or steroid metabolizing activity.

30. The method of claim 29, wherein the nucleic acid sequence operably linked to an enhancer element comprises a reporter gene, and wherein detecting xenochemical and/or steroid metabolizing activity comprises detecting the presence or absence of a product encoded by the reporter gene, and wherein presence of the product indicates that the test agent can activate a xenochemical and/or steroid metabolizing enzyme.

31. The method of claim 29, wherein the enhancer element is a xenochemical or steroid metabolizing enzyme enhancer element.

32. The method of claim 29, wherein the cell is a transformed cell.

33. A method of screening a sample suspected of containing a CAR-responsive steroid and/or xenochemical, comprising:

contacting a cell with the sample, wherein the cell comprises the polypeptide of claim 1 and a nucleic acid sequence operably linked to an enhancer element; and

detecting the presence or absence of steroid and/or xenochemical metabolizing activity.

34. The method of claim 33, wherein the nucleic acid sequence operably linked to an enhancer element comprises a reporter gene, and wherein detecting steroid and/or xenochemical metabolizing activity comprises detecting the presence or absence of a product encoded by the reporter gene, and wherein presence of the product indicates that the sample includes a CAR-responsive steroid and/or xenochemical.

35. The method of claim 33 wherein the enhancer element is a xenochemical or steroid metabolizing enzyme enhancer element.

Box No. VIII (iv) **DECLARATION: INVENTORSHIP (only for the purposes of the designation of the United States of America)**

The declaration must conform to the following standardized wording provided for in Section 214; see Notes to Boxes Nos. VIII, VIII (i) to (v) (in general) and the specific Notes to Box VIII (iv). If this Box is not used, this sheet should not be included in the request.

Declaration of Inventorship (Rules 4.17(iv) and 51*bis*.1(a)(iv))
for the purposes of the designation of the United States of America

I hereby declare that I believe I am the original, first and sole (if only one inventor is listed below) or joint (if more than one inventor is listed below) inventor of the subject matter which is claimed and for which a patent is sought.

This declaration is directed to the international application of which it forms a part (if filing declaration with application).

This declaration is directed to international application No. PCT/US03/05163 (if furnishing declaration pursuant to Rule 26*ter*).

I hereby declare that my residence, mailing address, and citizenship are as stated next to my name.

I hereby state that I have reviewed and understand the contents of the above-identified international application, including the claims of said application I have identified in the request of said application, in compliance with PCT Rule 4.10, any claim to foreign priority, and I have identified below, under the heading "Prior Applications," by application number, country or Member of the World Trade Organization, day, month and year of filing, any application for a patent or inventor's certificate filed in a country other than the United States of America, including any PCT international applications designating at least one country other than the United States of America, having a filing date before that of the application on which foreign priority is claimed.

Prior Applications:

I hereby acknowledge the duty to disclose information that is known by me to be material to patentability as defined by 37 C.F.R. § 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the PCT international filing date of the continuation-in-part application.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Citizenship: Japan

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Date: 3/21/03 (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26*ter* after the filing of the international application)

Name: UEDA, Akiko

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Date: 4/1/2003 (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26*ter* after the filing of the international application)

☒ This declaration is continued on the following sheet, "Continuation of Box No. VIII (iv)".

Sheet No. 2

Continuation of Box No. VIII (i) to (v) DECLARATION

If the space is insufficient in any of Boxes No. VIII (i) to (v) to furnish all the information, including in the case where more than two inventors are to be named in Box No. VIII (iv), in such case, write "Continuation of Box No. VIII..." (indicate the item number of the Box) and furnish the information in the same manner as required for the purposes of the Box in which the space was insufficient. If additional space is needed in respect of two or more declarations, a separate continuation box must be used for each such declaration. If this Box is not used, this sheet should not be included in the request.

Continuation of Box No. VIII (iv) DECLARATION: INVENTORSHIP

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Date: 3/21/03
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Date: 3/21/03
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Name: SUEYOSHI, Tatsuya

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Date: 3/21/03
(of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26*ter* after the filing of the international application)

Name:

Residence:
(city and either US state, if applicable, or country)

Mailing Address:

Citizenship:

Inventor's Signature:
(if not contained in the request, or if declaration is corrected or added under Rule 26*ter* after the filing of the international application. The signature must be that of the inventor, not that of the agent)

Date:
(of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26*ter* after the filing of the international application)

☐ This declaration is continued on the following sheet, "Continuation of Box No. VIII (iv)".

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(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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Declaration under Rule 4.17:
of inventorship (Rule 4.17(iv)) for US only

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WO 03/070915 A2

(54) Title: MUTATED CONSTITUTIVELY ACTIVE NUCLEAR ORPHAN RECEPTOR

(57) Abstract: Disclosed are constitutively active nuclear orphan receptors (CAR), which include one or more mutations which decrease the constitutive nature of CAR *in vitro*. The resulting non constitutively active nuclear orphan receptors can be used to screen for agents that metabolize xenochemicals and/or steroids.